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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	26

DATE MAILED: 02/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/576,858	Snyder et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Nov 27, 2002* .

2a) X This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *92-114* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *92-114* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____ .
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No.s)
4) Interview Summary (PTO-413) Paper No(s).
5) Notice of Informal Patent Application (PTO-152)
6) Other:

DETAILED ACTION

The amendment filed 11/27/02 has been entered. Claims 48, 54, 71-91 have been cancelled. Claims 92-114 have been added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 109 is objected to because of the following informalities: recitation of "and/or" in line 5 is improper grammar. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 92-99, 107, and 109-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 92-99 and 109-114 are directed to a method or pharmaceutical composition for "treating a blood disease or disorder" or a "coagulation defect," generically. Applicant has not indicated where the specification teaches treatment of a blood "disorder" or "coagulation defect". Pages 18-19 are cited, however, page 19, lines 12-13 teach using Factor IX coding sequence to treat hemophilia B, specifically, not a generic blood disease or disorder or coagulation defect.

The specification as originally filed does not support a method or pharmaceutical composition for treating any disease or disorder other than hemophilia B.

Claims 107 and 109-114 include the elements "a splice donor acceptor site or intervening sequence." Applicant has not indicated where the original specification supports these limitations. There does not appear to be support in the original specification for this broad limitation. The rAAV shown in Fig. 6 includes the MLV intervening sequence and its splice donor and acceptor sites as part of the MFG promoter, but this is mentioned only in passing and no importance is attached to the presence of the IVS in the MFG promoter. There is no general teaching of including an IVS or splice donor or acceptor sites in an rAAV of the originally described invention. Consequently, there is no evidence that applicant had contemplated these embodiments.

Claims 109-114 recite that the rAAV includes the structural gene and "an enhancer, promoter or both an enhancer and promoter", without reciting any particular relationship between them, i.e. the elements need not be operatively linked. There does not appear to be any support for this in the original specification, Applicant has not indicated where such support is to be found. Pages 24 -26 describes promoters being operably linked to the structural gene included in the rAAV.

Claims 92-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein the rAAV consists of AAV

terminal repeats flanking in order an MFG promoter (Moloney murine leukemia virus 5' LTR, adjacent MLV intervening sequence including the splice donor and acceptor sites and env ATG), a Factor IX coding sequence, and bovine growth hormone polyA sequence (i.e. the construct shown in Fig. 6), and wherein the mammal has hemophilia B, does not reasonably provide enablement for other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods of expressing a Factor IX encoded on any rAAV by transfecting the liver cells of a mammal (claims 100-108), and methods of and pharmaceutical compositions for treating a blood disease or disorder by expressing a Factor IX encoded on a rAAV by transfecting the liver cells of a mammal (claims 92-99 and claims 109-114, respectively). The claimed methods (and use of the claimed products) involve administration of a recombinant adeno-associated virus, rAAV, to liver cells either *in vivo*. Although the method of claims 100-108 is not limited to treatment of disease, the specification describes no other use for the claimed method, and there is no evidence of record identifying another well-established use for the general method. Therefore, in light of the specification claims 100-108 are interpreted as being implicitly directed to gene therapy, and are so evaluated for compliance of the specification with the enablement requirement. The implied use of this method to evaluate AAV as a suitable gene therapeutic vector does not meet the utility

requirement, and hence the enablement requirement for how-to-use, since such use would constitute using the invention for research on itself.

The specification provides general guidance limited largely to the listing of many diseases that may be treated, therapeutic transgenes, promoters and optional transcription termination sequences to be used to express the transgene but with little guidance as to which promoters or transcription termination sequences would be useful for which applications, a few methods of administration, and the teaching (see page 31, from line 15) regarding dosage and regimen of treatment that the skilled artisan should determine this by trial and error experimentation. While the claims embrace treating any blood disease or disorder or coagulation defect, the specification discloses only treating hemophilia B with a rAAV encoding Factor IX. It contains no guidance for treating any other disease or disorder. While some of the claims are limited to liver-specific promoters or enhancers, the specification does not teach that such promoters are more or less effective than promoters which are not tissue specific. The specification provides working examples only for transfer of rAAV that subsequently expresses human clotting factor IX under control of a MFG promoter and BGH polyA sequence to the liver of a healthy mouse *in vivo*. The MFG promoter is a constitutive retroviral viral promoter, not a liver-specific promoter. No working examples readable on the claims or of gene therapy are provided, nor are suitable model systems described except for the prophetic use of hemophiliac dogs for treatment with rAAV expressing factor IX. At page 10, lines 1-10 of the specification, it is stated that in such dogs retroviral vector-mediated gene therapy resulted in persistent, but subtherapeutic expression of

factor IX, while adenoviral-mediated gene therapy resulted in brief therapeutic expression, but that immunotoxicity of the vector results interfering with extended expression. These problems are cited as the impetus to develop AAV vectors for transduction of liver cells for gene therapy. There is no evidence presented in the specification that using AAV vectors would succeed, where retroviral and adenoviral vectors had failed. The working examples do not use an accepted model for treatment of hemophilia, or compare the use of an AAV vector to using a retroviral vector or adenoviral vector.

Gene therapy is a highly unpredictable and undeveloped art. Orkin et al. reviews the infant state of the art of gene therapy to just before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The instant application provides no guidance beyond the prior art, and offers no solutions to these problems raised by Orkin et al. Ross et al. (Hum. Gene Ther. 7: 1781-1790, 1996) indicates

in a follow-up of the Orkin report, that the situation had not changed up till the time the instant invention was made.

Orkin et al. provides little discussion on using AAV for gene therapy other than to say that little experience has been obtained due to the inability to produce large amounts of rAAV, which raises an issue of the suitability of AAV for gene therapy at the time the invention was made. The difficulty in preparing large amounts of rAAV for treatment is exacerbated by the low transduction efficiency. As taught by Russell et al. (Proc. Natl. Acad. Sci. USA 91: 8915-8919, 1994) it requires thousands of vector particles to transduce a single dividing cell *in vitro,* lacking immune mediators, mucous secretions, digestive enzymes and other potential inhibitors of transduction likely to be encountered *in vivo*. Consequently, it was unclear how effective rAAV would be in gene therapy (see Russell et al., page 8919, para. 1). With respect to rAAV vectors for use in gene therapy, the lack of experience in their use was an additional source of unpredictability at the time the instant invention was made.

Fisher et al. (J. Virol. 70(1): 520-532, 1996) describes experiments on using rAAV vectors to transduce liver cells *in vitro* and *in vivo.* The reference concludes that the low efficiency of rAAV transduction limits its usefulness as a gene therapy vector unless further advances are made because of the step of converting a single-strand rAAV to double-strand, which requires helper virus functions. In addition, expression of the transgene form a rAAV is influenced by factors other than the amount of double-strand rAAV, possibly requiring helper virus functions for efficient transport to and accumulation in the cytoplasm of transgene mRNA

The reference also discloses the difficulty in producing suitable quantities of purified rAAV particles. (See Fisher et al., Abstract, page 520 for overview; para. bridging pages 520-521; page 527, col. 1, para. 1; page 529, col. 1 through pages 531 and 532). Chen et al. (Hum. Gen. Ther. 8: 125-135, 1997) discloses that the efficiency of AAV vectors for transduction and expression of clotting factor IX in cultured cells was lower than for retroviral vectors both in terms of transduction and expression (see Abstract, page 125, for overview). A similar result was obtained by Koeberl et al. (Am. J. Hum. Genet. 57, suppl. 4: A43, 1995). Koeberl et al. (Proc. Natl. Acad. Sci. USA 94: 1426-1431, 1997) carried out experiments similar to those disclosed in the working examples with nearly the same rAAV vector but including a neo gene or using a different promoter (RSV) but no neo gene, and achieved sustained levels of factor IX expression comparable to those reported in the instant specification. The level of transduction was comparable to that using retroviral vectors, and required co-administration of wild type AAV and γ-irradiation to achieve. The reference teaches that plasma levels of 1-2 ng/ml FIX were far below therapeutic levels for humans of 100 ng/ml. As noted above, the specification teaches that retroviral delivery of a factor IX expression construct to hemophiliac dogs resulted in subtherapeutic expression. As shown by the art cited, rAAV delivery was not expected to be any better than therapeutically unsuccessful retroviral delivery without some further advance requiring inventive experimentation and development to improve rAAV transduction efficiency and transgene expression. Obtaining transgene expression from a rAAV delivered to the liver is not new. However, obtaining therapeutically relevant transgene expression would be. Those of

skill in this art, before and after the instant invention was made, recognized that rAAV transduction efficiency and transgene expression were insufficient to achieve therapeutic goals. The instant specification does not provide solutions to these problems except possibly the use of the MFG promoter.

In view of the unpredictable and undeveloped state of gene therapy as shown by the prior art, the minimal guidance in the specification on rAAV-mediated gene therapy in general and the lack of guidance specific for the treatment of specific diseases, the lack of relevant working examples, the high unpredictability of gene therapy in the art, and the inventive experimentation that would be required to overcome the problems known in the art, it would require undue experimentation in order to practice the invention as broadly claimed.

Applicant's arguments filed 11/27/02 have been fully considered but they are not persuasive on all points. The evidence presented by Applicant supports the view that the disclosed construct comprising a MFG promoter operably linked to the fIX coding sequence is enabled for treating hemophilia B. However, no evidence has been provided that would support enablement of the invention as broadly as claimed, which embraces any promoter or treatment of any blood disease or disorder, e.g. sickle-cell disease, hemophilia A (factor VIII deficiency), SCID, albuminemia, etc.

With respect to Snyder (1997), this reference was published after the filing date to which priority is being claimed and appears to include results that are presented in the instant specification. While it supports enablement of treating mice with hemophilia B with an rAAV

comprising a fIX coding sequence operably linked to a MFG promoter, it does not clearly support the broader invention instantly claimed, i.e. using other promoters and treating any blood disease in any mammal. At page 271, col. 1, the reference discloses that use of a similar rAAV containing the CMV promoter (another "constitutive" viral promoter) was unsuccessful. At page 274, col. 1, it concludes that while the results were encouraging, "further experimentation in larger animal models may be important to determine whether this type of delivery system will be successful in human clinical trials," which indicates that the general applicability of the method in other mammals was unpredictable.

With respect to Snyder (1999) published well after the filing date to which priority is being claimed, this reference provides evidence using hemophilia B mouse and dog models that administration of the rAAV consisting of a MFG promoter and BGH polyA sequence operably linked to fIX coding sequence produced therapeutic levels of fIX in these animals, which at least reduced the severity of the hemophilia and in some cases reversed it. However, it is noted that in both the mouse and dog model animals (page 66), pre-infusion with plasma from normal animals was required. While such a step is not taught in the instant specification, it is deemed that one of skill in this art would likely have considered it to be necessary due to the nature of hemophilia. The reference further teaches that success in animals other than rodents could not be predicted from success in mice (page 68, col. 1). While this reference supports enablement of the claimed embodiments wherein a MFG promoter is used and the disease is hemophilia B, it does not clearly support the broader invention instantly claimed.

Applicant takes issue with the citation of Koeberl et al. because the rAAV used was not identical to the rAAV exemplified in the instant specification (Fig. 6). However, the rAAVs and methods disclosed in Koeberl are embraced by the instant claims, and the claims are not limited to the construct shown in instant Fig. 6. Koeberl discloses two different rAAV encoding fIX; one consists of AAV terminal repeats flanking in order the MLV promoter (but lacking the adjacent MLV IVS), fIX coding sequence, SV40 promoter, neo coding sequence and SV40 polyA sequence, and the second consists of AAV terminal repeats flanking an RSV promoter, fIX coding sequence and AAV polyA sequence. Administration of both rAAV to mice (C57BL/6J) resulted in similar, sub-therapeutic levels of fIX expression, even with irradiation and administration of wild type AAV to increase transfection efficiency. Snyder (1997) disclosed another rAAV which had a CMV promoter in place of the MFG promoter, which also failed to yield therapeutic levels of fIX expression in mice. The MLV, RSV, and CMV promoters are all routinely used in putative gene therapy vectors. Taking Koeberl, Snyder (1997) and the instant specification together shows three unsuccessful constructs and only one successful construct. Thus, there is and was considerable unpredictability as to which specific rAAV would be successful. There are no teachings in the instant specification to indicate that the specific construct would be important for achieving therapeutic levels of expression in mice or any other mammal, nor does applicant offer any explanation as to why the one example disclosed in the specification succeeded while other similar rAAV failed. This suggests that the specific elements of the rAAV are critical to success, contrary to the general teachings of the specification.

Consequently, the instant specification does not generally enable using a generic rAAV which can express fIX in the context of the claims, but only the specific rAAV described by Fig. 3.

With respect to Harding et al. (2002), this reference was published well after the instant invention was made, and describes using a rat liver specific promoter that was not described in the instant specification. Consequently, it is unclear how one of skill in the art would have arrived at this method at the time the instant invention was made. With respect to Glader, this describes a proposed clinical trial, not a completed one. It does not include details on the vector used, e.g. it does not describe the promoter being used or other regulatory sequences included. Applicant has not indicated how it would follow from the instant specification.

In traversing the rejection under 35 USC 102(e) over Srivastava, Applicant argues that Srivastava is not enabling because it does not disclose how to make or how to use an rAAV carrying any of an unlimited number of transgenes, and because it does not teach that the factor VIII gene is too large to be packaged, and only includes working examples of galactosidase and globin. However, the same is true for the instant specification except for the difference in working example. Also, in the case of Srivastava, the working examples included a liver specific promoter, whereas the working examples of the instant application do not.

With respect to Lebrowski et al., Shenk et al., etc., it is not disputed that one of skill in the art knew how to prepare rAAV. Rather the prior art cited in the rejection teaches that known procedures, which would have included that of at least Lebrowski and probably Shenk, were in

general inadequate for producing sufficient quantities of a therapeutic rAAV. The amount of virus required for treating mice would clearly be much less than for larger animals.

With respect to Kessler and Okada, these references are directed to other types of rAAV mediated therapy, not treatment of hemophilia B. Orkin taught that gene therapy for each disease would present its own scientific and clinical challenges, which indicates that one cannot extrapolate from a gene therapy method for one disease to predict what would or would not be successful for a different disease.

Claims 96, 103, 107, 112 and 113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 96, 103 and 112 each recite the limitation "the MFG promoter". There is insufficient antecedent basis for this limitation in the claim; "the" should be replaced with --a--.

Claim 107 is indefinite due to the poor grammar reciting the list of elements with a mixture of conjunctions separating some of the terms. It is unclear whether these are all alternatives, or whether there are two classes of elements - promoter/enhancer and splice donor acceptor site/intervening sequence . It is unclear whether "a splice donor acceptor site or intervening sequence" must be present or not; neither is recited in claim 100. It is also unclear what "a splice donor acceptor site" is, it does not appear to be defined in the specification.

Claim 113 recites the limitations "the albumin promoter", "the α fetoprotein promoter", "the α fetoprotein enhancer", "the human apolipoprotein E (ApoE) promoter", "the AI apolipoprotein liver-specific enhancer", and "the α1 antitrypsin promoter" in lines 2-5 . There is insufficient antecedent basis for this limitations in the claim.

Claim Rejections - 35 USC § 102

Claims 100, 101, 104 and 105-107 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Srivastava et al. (US 2001/0051611 A1).

See entire document, e.g. Abstract, paragraphs 0008, 0009, 0013, 0015, 0016, 0023, 0025, 0033-0035, 0048-0051, claims 1-11. The instant claims require only liver expression of fIX, not therapeutic expression. Claim 107 is included due to the ambiguity as to whether "a splice donor acceptor site or intervening sequence" is required or is an alternative to a promoter, enhancer or both.

Applicant's arguments filed 11/27/02 have been fully considered but they are not persuasive. It is asserted that Srivastava does not provide an enabling disclosure because it does not disclose how to make or how to use an rAAV carrying any of an unlimited number of transgenes, and because it does not teach that the factor VIII gene is too large to be packaged, and only includes working examples of galactosidase and globin.

However, Srivastava does provide general guidance on how to make the rAAV and how to administer them for therapy and what transgenes to include for treating various diseases in

paragraphs 0014-0037 and the illustrative examples. While this guidance may or may not be sufficient for treating hemophilia (in view of the enablement rejection set forth above), there is no evidence that one would not obtain some fIX expression, which is all the rejected claims require. With respect to factors VIII, para. 0023 teaches that the mini-gene should be used, and does not teach to use the full length coding sequence. Also, this point is irrelevant to the instant claims. The general guidance in Srivastava is very similar to that presented in the instant specification, and were the instant specification applied as prior art, one might have made the same statements concerning it. The fact that Srivastava is not a patent is irrelevant. See MPEP 2121.

With respect to the priority of Srivastava to provisional applications 60/025,616 and 60/025,649, the provisional applications have been reviewed and US 2001/0051611 is entitled to the priority. The '616 application is identical, including the claims, to the publication except it lacks Figure 4, paragraph 0041 describing Fig. 4, and para. 0081 describing deposit information. The '649 application is identical, including the claims, to the publication except it lacks Figure 4, paragraph 0041 describing Fig. 4, and the third and fourth sentences of para. 0081. The supporting information for Fig. 4 and para. 0041 are present in Example 5, which is present in the provisional applications.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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